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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/337,746	06/22/1999	GREGORY M. GLENN	PM-254811	9348

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EXAMINER
EWOLDT, GERALD R

ART UNIT	PAPER NUMBER
1644	19

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/337,746	Glenn et al.
Examiner	**Art Unit**
G. R. Ewoldt	1644

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *1/07/00, 5/24/00, 6/08/01. and 10/10/01* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-69* is/are pending in the application.

4a) Of the above, claim(s) *43-52* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-42 and 53-69* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
18) ☐ Interview Summary (PTO-413) Paper No(s). _____
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

1. Applicant's election with traverse of Group I, Claims 1-29, 33-38, 40-42, 45, and 47-69, and the species:

A) antigen - *E. coli* heat-labile enterotoxin (LT),

B) molecular weight - greater than 1000 D,

C) targeting molecule - LT,

in Paper No. 18 is acknowledged. The traversal is on the grounds that the methods of inducing an immune response employing various antigens should be examined together. Upon further consideration, it is the Examiner's position that the various pathogenic antigens, i.e., viral, bacterial, fungal, properly belong in a single group. However, it is still the Examiner's position that methods of inducing an immune response employing tumor antigens or autoantigens are patentably distinct. The search has been expanded accordingly.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 43-52 are withdrawn from further consideration by the examiner, 37 C.F.R. § 1.142(b) as being drawn to nonelected inventions.

Claims 1-42 and 53-69 are being acted upon.

3. The reference in the first line of the specification must be updated to indicate the status of prior applications 08/896,085, now U.S. Patent No. 5,980,898.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-42 and 53-69 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for,

a method for transcutaneous immunization (TCI) comprising applying a formulation that does not include a heterologous adjuvant to intact skin, said formulation consisting of cholera toxin (CT), LT, or *Pseudomonas exotoxin A* (ETA), to hydrated skin does not reasonably provide enablement for,

A) a method for TCI comprising applying a formulation comprised of an antigen, wherein said formulation does not include a heterologous adjuvant to intact skin,

B) a method for TCI comprising activating at least one antigen presenting cell underlying where the formulation's site of application,

C) a method for TCI comprising an APC wherein the APC is a Langerhans cell,

D)a method for TCI comprising applying an antigen in whole cell form,

E)a method for TCI comprising applying an antigen comprising a viral particle or virion,

F)a method for TCI comprising applying diphtheria toxin (DT),

G)a method for TCI wherein the induced immune response recognizes a lipopolysaccharide (LPS).

H)a method for TCI wherein the induced response recognizes influenza virus hemagglutinin (HA), influenza virus nucleoprotein (NP), Hemophilus influenza B polysaccharide conjugate (Hib-PS), and *Escherichia coli* colonization factor CS6.

I)a method for TCI wherein underlying endosomes or lysosomes are lysed.

The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation. The scope of the claims are not commensurate with the enablement provided by the disclosure with regard to the breadth of the claims.

It is disclosed in the Background section of the specification the claimed invention is based on unexpected findings, and that one of skill in the art would not previously have expected the claimed invention to work. See for example page 5:

> "Paul and Cvec (1995) stated that it is "impossible to immunize epicutaneously with simple peptide or protein solutions." Thus, transcutaneous immunization as described herein would not be expected to occur according to this group,"

Accordingly, the specification discloses 62 examples in support of the claimed invention. However, it is noted that in the 62 example, just 4 closely related embodiments of the actual claimed invention (TCI employing a formulation that does not comprise an additional adjuvant) are disclosed (CT, LT, ETA, and TT). Of the 4 embodiments, the disclosed data indicates that CT, LT, and ETA

may function as claimed, however, the data for TT are at best inconclusive, and thus, insufficient to support the use of the TT formulation in the method of the instant claims.

The instant claims consist of a single independent claim and 58 dependent claims reciting specific limitations and or characterizations of the claimed method. In general, the specification provides insufficient support for the additional specific limitations and or characterizations of the claimed method.

Regarding A and F), a method for TCI comprising applying a formulation comprised of an antigen, wherein said formulation does not include a heterologous adjuvant to intact skin and a method for TCI, comprising DT. The specification discloses just 3 closely related functional embodiments (CT, LT, and ETA) as well as numerous nonfunctional embodiments (any antigen that does not induce an immune response without heterologous adjuvant, i.e., DT or CS6). It is noted that the 3 functional embodiments of the claimed invention comprise closely related bacterial formulations. The specification fails to disclose any functional bacterial formulations other than the 3 toxin-based formulations discussed above. Additionally the specification discloses no functional viral, fungal, or parasite-derived formulations. Thus, given the unexpected nature of the method of the claimed invention, embodiments employing formulations other than CT, LT, and ETA, must be considered highly unpredictable; said invention would then require undue experimentation to practice as claimed. Note, regarding DT, the specification appears to use the same abbreviation for both diphtheria toxin and diphtheria toxoid, two compositions with presumably different properties.

Regarding B, C, and I), a method for TCI comprising activating at least one antigen presenting cell underlying the formulation's site of application, a method for TCI comprising an APC wherein the APC is a Langerhans cell, or a method for TCI wherein underlying endosomes or lysosomes are lysed, the claims assert specific aspects of a mechanism by which the claimed method might function, in particular, aspects involving the antigen presentation and Langerhans cells. The specification, however, discloses just 2 Examples (17 and 18) in support of the claims. Example 18 is prophetic (and thus discloses no results) while Example 17 discloses only that, upon crude superficial examination after CT application, Langerhans cells appear to express higher levels of MHC Class II and changes in cell morphology. The specification further discloses that the results "may be confirmed using flow cytometry," which indicates that the

disclosed "results" are at most, preliminary. Therefore, Example 17 provides insufficient support for the claimed limitations regarding an asserted mechanism by which the claimed invention functions.

Regarding D and E), a method for TCI comprising applying an antigen in whole cell form or a method for TCI comprising applying an antigen comprising a viral particle or virion, if said methods were enabled, said methods would essentially mean that the skin provides no protection to whole cells or viruses at all (as said cells or viruses would pass through the skin) and that a subject would become infected or immunized to all cells or viruses to which said subject came in contact. It is well-known in the immunological arts that subjects are neither immunized nor infected after skin contact with most pathogenic cells or viruses, e.g., HIV. Thus, the invention as broadly claimed, must be considered highly unpredictable; said invention would then require undue experimentation to practice as claimed.

Regarding G) a method for TCI wherein the induced immune response recognizes a LPS, while LPS is a known antigen and adjuvant, the specification fails to disclose that LPS passes through the skin in the absence of a carrier such as CT. Again, given the unexpected nature of the claimed invention, mere assertion of the claimed method comprises insufficient support and must be considered highly unpredictable; said invention would then require undue experimentation to practice as claimed.

Regarding H), a method for TCI wherein the induced response recognizes influenza viruss HA, influenza virus NP, Hib-PS, and *E. coli* CS6, the specification provides insufficient support that any of the claimed inducers might function in the claimed method, and indeed provides evidence that at least one of said "inducers" actually can not function in the claimed method. See Example 33 where it is disclosed that "Administration of the antigen (CS6) alone failed to induce a rise in antigen specific antibody levels when compared to the levels observed in prebleed samples." Thus, the invention as broadly claimed, must again be considered highly unpredictable; said invention would again require undue experimentation to practice as claimed.

In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Thus, in view of the quantity of experimentation necessary, the lack of sufficient working examples encompassing the entirety of the claimed methods, the unpredictability of the art, the lack of

sufficient guidance in the specification, and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

6. Claim 58 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

There is insufficient written description to show that Applicant was in possession of a conjugate comprising an antigen and a heterologous molecule which targets an antigen presenting cell. Given the definition of an adjuvant as a substance that "potentiates an antigen-specific immune response," the specification fails to disclose any "heterologous molecules which target an antigen presenting cell" that would not also comprise adjuvants (as required by the negative limitation of Claim 1). Given the apparently impossible nature of the claim, one of skill in the art must conclude that the specification fails to disclose a representative number of species to describe the claimed genus. See *Eli Lilly*, 119 F.3d 1559, 43 USPQ2d 1398.

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between functionand structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. On the other hand, there may be situations where one species adequately supports a genus. What constitutes a "representative number" is an inverse function of the skill and knowledge in the art. Satisfactory disclosure of a "representative number" depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. For inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species *can not* be achieved by disclosing just a single species within the

genus. Description of a representative number of species does not require the description to be of such specificity that it would provide individual support for each species that the genus embraces. If a representative number of adequately described species are not disclosed for a genus, the claim to that genus must be rejected as lacking adequate written description under 35 USC 112, 1st paragraph.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claim 10 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, it is unclear just what is being "hydrated" in the claim.

9. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321c may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

10. Claim 64 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 6 of copending Application No. 09/545,417. Although the conflicting claims are not identical, they are not patentably distinct from each other. The claims of the instant application recite a method of TCI comprising applying a dry formulation that does not include a heterologous adjuvant to intact skin. Claim 6 in the '417 application recites a method of inducing an immune response comprising applying a dry

formulation of an ADP-ribosylating exotoxin. Said exotoxins comprise antigens capable of TCI that do not include a heterologous adjuvant. The methods are therefore not patentably distinct.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

11. No claim is allowed.

12. Applicant's Form 1449's, submitted 1/07/00, 2/24/00, and 6/08/01, comprising IDS's of approximately 300 references, have not been initialed because said references have not been provided. While some of the references may have been provided in previous applications, said references are unavailable to the Examiner.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Gerald Ewoldt whose telephone number is (703) 308-9805 The examiner can normally be reached Monday through Thursday from 7:30 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

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